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Maximization of regioselectivity in hydroformylation of vinyl-aromatics using simple factorial design

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Abstract

The importance of hydroformylation reactions for fundamental organic and industrial synthesis has prompted a detailed analysis of the factors governing the regioselectivity of these processes. A simple 2^k factorial design has shown that a very significant increase in the regioselectivity of vinyl-aromatics (typically from 70% to more than 98%) can be obtained by the exclusive manipulation of two variables, pressure and temperature, within the usual working values for such variables. It is also shown that optimised values can be obtained from within a range of possible values. The role of the ligand in the overall response of the system is also discussed and analysed.

Keywords: Factorial design; Hydroformylation; Regioselectivity

1. Introduction

It is believed that the main goal of rhodium-catalysed hydroformylation of vinyl substrates is to control the reaction regioselectivity between the two possible types of aldehydes (branched or linear). The hydroformylation mechanism [1,2] was intensively studied by high pressure in situ IR, NMR and also by deuteroformylation experiments [3]. From these studies, it is accepted that the equilibrium between the branched and linear alkyl–metal intermediates can be modulated by substrate structure and reaction parameters, pressure and temperature (Scheme 1).

The key step on the hydroformylation mechanism that determines regioselectivity is the alkene insertion into Rh–H bond giving the alkyl–metal intermediates. This step can be reversible or irreversible and the formation of linear and branched aldehydes is then dependent of the reaction conditions (Scheme 1).

The use of vinyl-aromatic substrates nominated styrene [4], vinylpyrroles [5] and vinylpyridines [6] clearly favours the formation of branched aldehyde due to the stabilization of the branched-alkyl–rhodium intermediate by the aromatic group, but the linear aldehyde is in general present. The optimization of the hydroformylation regioselectivity has usually been focused on a very simplified approach, i.e. if pressure is varied, temperature is maintained constant during the experiment. Essentially, this procedure intends to avoid pressure/temperature interaction that may affect regioselectivity in an unpredictable way.

However, there are a number of computational tools that allow factor analysis on 'black box' systems, i.e., systems that are either intrinsically too complex to have a physically motivated functional form governing the system response or responses, or in which the way factors act is altogether unknown. Factorial design is one of such tools, and allows a systematic change of the several variables [7]. This and other types of experimental design are currently applied in a number of areas, such as pharmaceutical industry [8], some processes in chemical engineering [9], catalysis [10] and analytical chemistry [11]. In hydroformylation reactions, and to our knowledge, 2^k-factorial experimental design has been essentially used to identify significant factors that can influence the overall yield of the reaction [12].

The purposes of factorial design are essentially to (i) identify the most relevant factors, (ii) rationalise their impact in the process and the way they interact and (iii) use its prediction ability to choose optimal values for the process variables. Naturally, these purposes suggest that a significant, although not excessive, number of factors should be present to extract the full potential of the technique. However, it will be shown that even for a very

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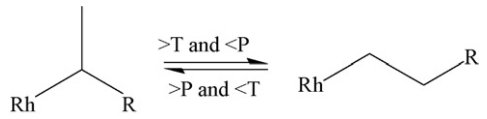


Scheme 1.

small number of degrees of freedom and, consequently, for an extremely low number of preliminary experiments, a significant improvement in the process may be obtained.

The objective of the present study is to optimise the regioselectivity in the rhodium catalysed hydroformylation of styrene and a divinylporphyrin, dimethyl ester protoporphyrin-IX, in the presence of different ligands. In the first case, the diphosphines dppe (1,2-bis(diphenylphosphyne) ethane) and dppp (1,3-bis(diphenylphosphine) propane) were tested, while for the divinylporphyrin, PPh_3 (triphenylphosphine) was selected. Choosing pressure and temperature as control variables, a simple 2^k factorial design has allowed obtaining regioselectivity values close to 100%. Note that, in some cases, values of the order of 90% had already been obtained in preliminary experiments. Even in those cases, a significant increase was achieved. It should be stressed the relevance of such optimization in pharmaceutical industrial processes, for which in most cases the presence of a minute amount of by-products is highly undesirable. Additionally, coded values for the variables were used in a further effort to rationalise the dependence of these hydroformylation reaction in the imposed conditions. We have also analysed the effect of ligand and the respective interaction with pressure and temperature.

2. Experimental

2.1. Chemicals and equipments

^{1}H spectrum was recorded in $CDCl_3$ solutions on a Bruker Avance 300 spectrometer, operating at 300.13 MHz. GC was carried out on an Agilent 6890 series equipped with capillary Agilent HP5 column (30 m). $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ was synthesized by a slightly modified procedure with respect to the described in the literature [13]. The phosphorous ligands dppe, dppp and PPh_3 were purchased from Aldrich. Styrene and protoporphyrin-IX were purchased from Aldrich and the latter one was then derivatized to the corresponding dimethyl ester according to our previously described procedure [14].

2.2. General hydroformylation procedure

The hydroformylation reactions were carried out following the process described in refs. [14,15].

The autoclave was purged by three cycles with vacuum and *syn*-gas. Being in vacuum, the phosphorus ligand, the vinyl-aromatic substrate and $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$, dissolved in toluene, were introduced through the inlet cannula. The autoclave was then pressurized with the *syn-gas* pressure at the working temperature presented in Tables 1, 3 and 7. The regioselectivities were determined by GC for styrene experiments or by ^{1}H NMR for dimethyl ester of protoporphyrin-IX, after solvent evaporation.

2.3. Experimental design

The optimization of the regioselectivity of hydroformylation reaction was performed using a full 2^2 factorial design following standard methodology (see, e.g. refs. [7,8]) using pressure (P) and temperature (T) as experimental variables.

Two levels were thus employed for each variable, which results in just four experiments for each system. The objective function is,

$$\%\text{regio} = a_0 + a_P P + a_T T + a_{PT} PT \quad (1)$$

where %regio denotes the percentage of branched aldehyde; it includes the direct effect of each control variable and the respective interaction.

The polynomial and response surfaces were worked out through the software STATISTICA 6.0 (StatSoft, Tulsa/OK, USA).

A full 2^3 factorial design with two levels for pressure, temperature and ligand was also built, for the styrene hydroformylation reactions, to further rationalize the results obtained with the simpler designs.

3. Results and discussion

In what follows we will discuss the use of 2^2 factorial design in the rhodium catalysed hydroformylation reaction of two different vinyl aromatic systems, namely styrene and dimethyl ester of protoporphyrin-IX. In the first case, the diphosphines dppe and dppp were tested as ligands, while for the latter, PPh_3 was selected. These reactions are essentially controlled by three major factors: pressure, temperature and ligand structure. Usually, when a sufficient amount of ligand is used, a single catalytic active species is obtained. This means that, in principle, only a small set of design experiments is required for the full factorial design. In summary, these reactions are excellent candidates for previous optimization of the reaction conditions resorting to simple design procedures.

3.1. 2^k Factorial design in the hydroformylation of styrene

The first application that we describe corresponds to the hydroformylation of styrene in two different catalytic systems, with the structurally related diphosphines depicted in Fig. 1. The reaction regioselectivity was analysed, for each of the catalytic

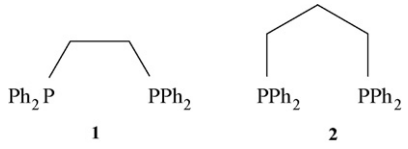


Fig. 1. Structure of ligands: dppe [1,2-bis(diphenylphosphine) ethane] 1and dppp [1,3-bis(diphenylphosphine) propane] 2.

Table 1
Choice of level and experimental results for the regioselectivity in the styrene hydroformylation reaction, using ligand 1

Entry[a]	P (bar)[b]	T (°C)	Branched aldehyde (%)[c]
1	8	65	72.4
2	8	80	67.4
3	30	65	90.0
4	30	65	90.2
5	30	80	87.0
6	30	80	86.7

[a] Catalytic system: dppe 1/$Rh_2(\mu\text{-}OMe)_2(cod)_2$/ = 1.2, reaction time: 12 h.
[b] CO/H_2 (1:1).
[c] GC determinations.

systems studied, in what concerns the effect of pressure and temperature.

The first system addressed uses dppe (1,2-bis(diphenylphosphyne)ethane) 1, as ligand. We have obtained the 2 factor-2 level results shown in Table 1.

These can be translated by the first order linear model with interaction, using Eq. (1) and data from Table 1,

$$\%\text{regio} = 90.4 + 0.46P - 0.38T + 0.005PT \quad (2)$$

In Fig. 2, we represent the response surface as a function of effects, temperature and pressure, using the above model. It is observed that, for the considered range, the effect of pressure is more important than that of temperature. When the pressure is increased from 6 to 34 bar, at the maximum temperature, $T = 60\,^{\circ}C$, it is observed an increased in the yield of branched aldehyde from 72 to 95%. However, if the pressure is kept at 34 bar, a variation of temperature from 20 to 60 °C determines a decrease in the percentage of branched aldehyde from 100 to 95%.

For this choice of limiting operational conditions, it is seen not only that, globally, pressure is more important for the specific catalytic system, but also the interaction between the two factors is relatively low, thus not affecting the system response.

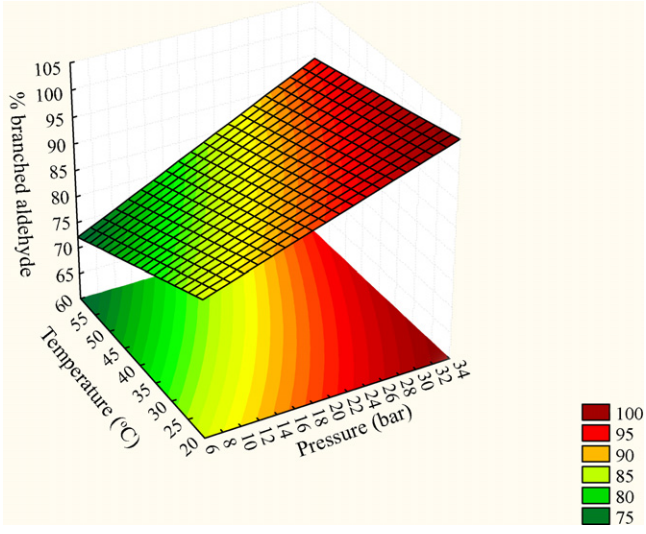


Fig. 2. Three-dimensional representation of the response surface from Eq. (2), corresponding to ligand 1.

Table 2
Values of coefficients, and the respective t and probability, in percentage, for a Student's t-test

Coefficient	Value	t	Probability (%)
a_0	79.2	1014	>99.9
a_P	9.3	119	>99.9
a_T	−2.1	26	99.9
a_{PT}	0.44	6	97

All data pertain to Eq. (1), using coded (−1, +1) variables, for the hydroformylation of styrene with ligand 1.

Using coded variables, −1 and +1, for the lowest and highest values of P and T, respectively, we obtain the results depicted in Table 2. It also includes the value of t and the %probability for the significance of each parameter in a Sudent's t-test [7]. It is shown a clear dominance of pressure and a low value of the interaction coefficient (a_{PT}). The latter presents, also, the lowest significance (although corresponding to a probability above 95%).

The next step is to predict the optimal conditions so as to obtain 100% regioselectivity in the hydroformylation of styrene, using diphosphine 1 as ligand. For this, a straightforward procedure is employed. Eq. (2) is rewritten so that a relationship between pressure and temperature is achieved for %regio = 100 (see Fig. 3).

Values higher than 100% are thus discarded so as to limit the range of choice for the variables. From Fig. 3, it is concluded that the optimal conditions are located within 3–52 °C and 25–40 bar for the considered ligand. Using results from Fig. 3, we have selected $T = 25\,^{\circ}C$ at $P = 32$ bar to be used in further experiments. These conditions increased the regioselectivity for the branched aldehyde to ca. 97%.

In order to assess the influence of ligand structure in the factorial analysis, experiments were also conducted using the dppp 2 as ligand (Fig. 1).

Again, using Eq. (1) to describe the system response and the data from Table 3, we obtain

$$\%\text{regio} = 205.09 - 2.42P - 1.92T + 0.043PT \quad (3)$$

Eq. (3) is depicted in Fig. 4, as a function of the effects of pressure and temperature.

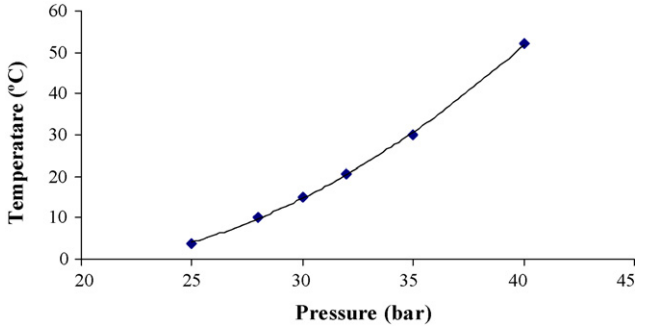


Fig. 3. Projection of the %regio = 100 line onto the pressure/temperature plane. Results correspond to the hydroformylation of styrene using diphosphine 1 as ligand.

Table 3
Choice of level and experimental results for the regioselectivity in the styrene hydroformylation reaction, using ligand 2

Entry[a]	P (bar)[b]	T (°C)	Branched aldehyde (%)[c]
1	8	65	83.0
2	8	80	59.3
3	30	65	91.2
4	30	80	81.4
5	30	80	82.0

[a] Catalytic system: dppp 2/$Rh_2(\mu\text{-}OMe)_2(cod)_2$ = 1.2, reaction time: 12 h.
[b] CO/H_2 (1:1).
[c] GC determinations.

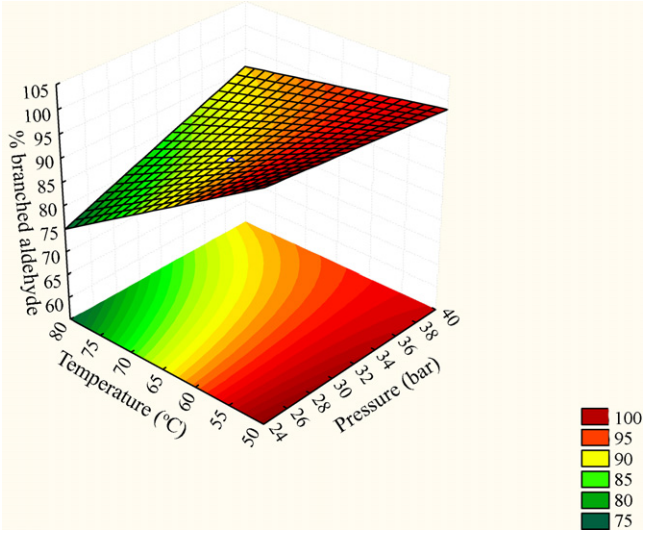


Fig. 4. Three-dimensional representation of the response surface from Eq. (3), corresponding to ligand 2.

It is observed that, once again, regioselectivity increases for low temperatures (52 °C) and high pressure (24–40 bar). The effect of factors is now mutually correlated. When the pressure is increased from 24 to 40 bar, at the maximum temperature 80 °C, the percentage of branched aldehyde goes from 75 to 92% (Fig. 4). For a pressure of 24 bar, an increase in temperature from 50 to 80 °C results in a decrease in the formation of branched aldehyde from 95 to 75%. This analysis allows us to conclude that both pressure and temperature affect the system response. However, irrespective of pressure in the 50–55 °C temperature range, the %regio is clearly higher (>95%).

As for ligand 1, results with coded variables are shown in Table 4. The similarity between the effects of temperature and

Table 4
Values of coefficients, and the respective t and probability, in percentage, for a Student's t-test

Coefficient	Value	t	Probability (%)
a_0	78.8	397	99.8
a_P	7.7	39	98.3
a_T	−8.3	42	98.5
a_{PT}	3.6	18	96.4

All data pertain to Eq. (1), using coded (−1, +1) variables, for the hydroformylation of styrene with ligand 2.

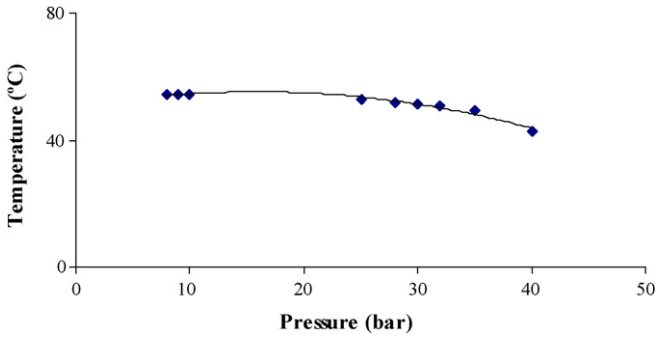


Fig. 5. Projection of the %regio = 100 line onto the pressure/temperature plane. Results correspond to the hydroformylation of styrene using diphosphine 2 as ligand.

pressure and the large value of the interaction confirm previous observations. Note, additionally, the negative value of a_P in Eq. (3), which is positive in the coded expression (Table 4). The latter value, more directly reflects the fact that %regio tends to increase with pressure in the working range.

We proceed as above to establish optimal reaction conditions in the use of diphosphine 2 system. The %regio = 100 cut on the pressure/temperature plane is found in Fig. 5.

The ideal conditions for obtaining 100% of branched aldehyde (ligand 2) are found for a broad range of pressure (10–40 bar), but a very limited range of temperature (50–55 °C). Again, the rate of reaction regioselectivity is strongly affected by temperature. Optimal test conditions are thus chosen for P = 40 bar and T = 40 °C. These conditions allowed to an increased on the percentage of branched aldehyde to 95.

Differences are very clear in the effects of pressure and temperature upon regioselectivity resorting to ligands 1 and 2. For ligand 1, the effect of pressure is considerable, with temperature playing a minor role while, for ligand 2, both factors affect regioselectivity. These observations are in accordance with the mechanism proposed for hydroformylation reactions [2]. In this mechanism, the fundamental step for establishing the degree of regioselectivity is the insertion of the alkene in the Rh–H bond, originating the metal–alkyl intermediate species. The reversibility or not of this step originates the formation of one of the two aldehydes (linear and branched). For low CO pressures and high temperatures, the reversible process, elimination, is favoured and so the formation of the linear aldehyde too. There are also evidences that regioselectivity is also affected by the nature of the substrate. In the case of functionalized substrates, for example vinyl-aromatics, the regioselectivity is significantly affected by resonance stabilization of the aromatic ring [16].

The analysis will now be enlarged using two levels for the ligand, ligand 1 (−1) and ligand 2 (+1), in a full 2^3 design with coded variables. The new function now comprises an additional coefficient for the direct effect of the ligand, a_L, and two new interaction terms, a_{LP} and a_{LT}, in an obvious notation (see Table 5). Additional conclusions can be drawn from this three-factor approach. Pressure and temperature are important variables in the process, but the direct effect of the ligand is negligible: the respective coefficient cannot be distinguished from zero. However, the effect of the ligand is, clearly

Table 5
Values of coefficients, and the respective t and probability, in percentage, for a Student's t-test

Coefficient	Value	t	Probability (%)
a_0	79.1	95.7	>99.9
a_P	8.5	10.3	>99.9
a_T	−5.3	6.4	99.7
a_L	−0.1	0.1	5.6
a_{PT}	1.8	2.2	90.3
a_{TL}	−2.7	3.4	97.2
a_{LP}	−0.6	0.7	49.9

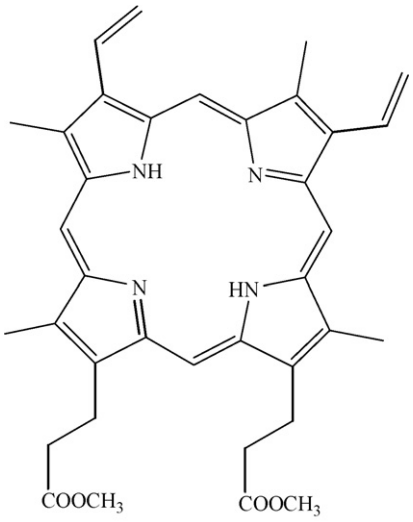
All data pertain to Eq. (1), using coded (−1, +1) variables, for the hydroformylation of styrene, including variations in ligands.

dependent on the temperature as can be extracted from the interaction coefficient a_{LT}, while the interaction with pressure is less significant, a_{LP}. The two ligands display similar bite angles (ca. 80.5 and 85.5° for ligands 1 and 2, respectively), and both give rise to equatorial–axial complexes with the metal and so the low absolute value of the a_L coefficient is not surprising. A visible interaction between ligand structure and temperature, a_{LT}, can be related to the differential flexibility of the two chelate rings [17].

A standard analysis using ANOVA [8] was also carried out on this design (Table 6). It indicates that, although the model is not fully adequate, it is still highly significant and explains the major part of the deviations from the corresponding mean values.

3.2. 2^2 Factorial design in the hydroformylation of dimethyl ester protoporphyrin-IX

The functionalization of porphyrins is an area of growing interest due to their multiple applications especially for therapeutical and diagnostic medical applications [18]. Recently, we described the synthesis of formyl dimethyl ester protoporphyrin-IX [14] via hydroformylation reaction. The optimization of the regioselectivity using a univariate approach by changing pressure or temperature, conducted to the formation of 90% of regioselectivity for the branched aldehyde (Table 7). In order to extend the previous study to the asymmetric hydroformylation reaction it is extremely relevant to maximize the regioselectivity for the branched aldehyde. To achieve this goal we applied again the 2^2 factorial design described above to the hydroformylation reaction of dimethyl ester of protoporphyrin-IX 3 (Fig. 6) selecting again pressure and temperature as factors to optimize, using rhodium/triphenylphosphine as catalytic system.



3

Fig. 6. Structure of dimethyl ester of protoporphyrin-IX.

To implement the 2^2 factorial design, two levels of pressure (3 and 30 bar) and two levels of temperature (40 and 80 °C) have been selected. Results for the experimental regioselectivity of the branched aldehyde are presented in Table 7.

The mathematical model of Eq. (1), as applied to this system, produced

$$\%\text{regio} = 90.40 + 0.63P - 0.41T - 0.002PT \quad (4)$$

The graphical representation of the response surface, as a function of pressure and temperature, is shown in Fig. 7.

From the analysis of this figure, it is seen that, in this specific catalytic system, the formation of the branched aldehyde increases linearly with the decrease of temperature and increase of pressure. The observations resulting from these empirical analysis are again in good agreement with the mechanistic proposal for catalytic hydroformylation reaction of styrene (high pressure and low temperatures favours the regioselectivity for the branched aldehyde) [2].

Table 8 shows the results corresponding to the use of coded values in Eq. (1). The same order of magnitude for the effects of pressure and temperature, and a less significant interaction term are the main results.

Eq. (4) is rewritten so that a relationship between pressure and temperature is achieved for %regio = 100, shown in Fig. 8.

Table 6
Analysis of variance of the regression in Table 5

	Degrees of freedom	Sum of squares	Mean square	F	Significance (%)
Total	10	1057.5			
Regression	6	1030.4	171.7	190.8	<0.1
Residual	4	27.1	6.8		
Lack of fit	1	24.4	24.4	27.2	<5
Pure error	3	2.7	0.9		

Table 7
Choice of level and experimental results for the regioselectivity of dimethyl ester of protoporphyrin-IX hydroformylation reaction, using PPh_3 as ligand

Entry[a]	P (bar)[b]	T (°C)	Branched aldehyde (%)[c]
1	3	40	76.1
2	3	40	75.5
3	3	80	59.3
4	30	40	90.5
5	30	80	71.3
6	30	80	72.0

[a] Catalytic System: 1.69×10^{-2} mmol of 3, toluene (6 mL), reaction time: 18 h. Subst/Rh = 50; PPh_3/Rh = 1.2.
[b] CO/H_2 (1:1).
[c] values obtained by ^1H NMR.

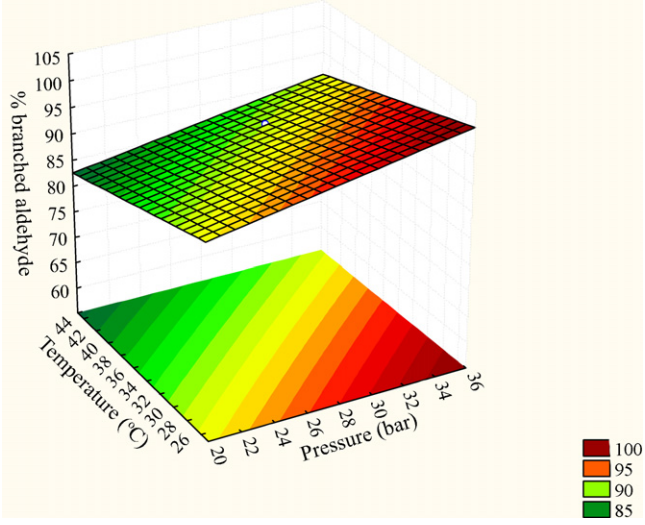


Fig. 7. Three-dimensional representation of the response surface from Eq. (4), corresponding to the hydroformylation reaction of 3.

Optimal values for the hydroformylation reaction of 3, are thus located between 10 and 45 °C and 18–50 bar. We have selected the point 40 bar, 31 °C. We recall that low temperatures result in very low reaction rates. These values were applied experimentally and the percentage of branched aldehyde obtained was 98, after 18 h. This again constitutes a significant improvement in the degree of regioselectivity.

Table 8
Values of coefficients, and the respective t and probability, in percentage, for a Student's t-test

Coefficient	Value	t	Probability (%)
a_0	74.3	263	99.8
a_P	6.8	24	97.3
a_T	−8.8	31	98.0
a_{PT}	−0.6	2	71.5

All data pertain to Eq. (1), using coded (−1, +1) variables, for the hydroformylation of dimethyl ester of protoporphyrin-IX 3.

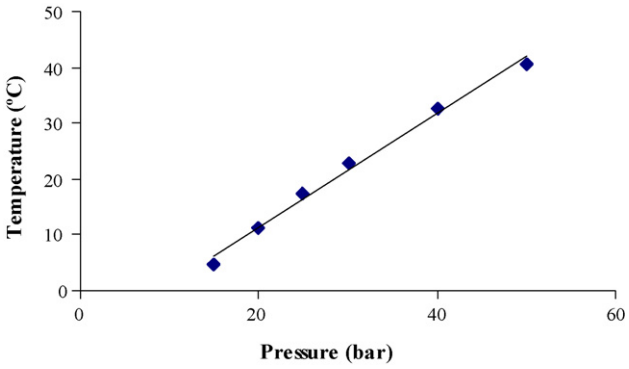


Fig. 8. Projection of the %regio = 100 line onto the pressure/temperature plane. Results correspond to the hydroformylation of porphyrin 3.

4. Conclusion

The application of 2^2 factorial design in a set of hydroformylation reactions has shown that this simple approach, resorting only to two factors – pressure and temperature – not only provides the basis for rationalising results with different ligands, but is also very useful for the prediction of optimal operational conditions. While in most cases factorial design is used to assess the importance of a number of factors in black-box processes, it is seen that in these hydroformylation reactions only four experiments provide a large insight and may be fine-tuned.

We have also used a 2^3 full factorial design comprising pressure, temperature and ligand for the catalytic hydroformylation of styrene. The importance of pressure and temperature was stressed. Also, it was shown that for the structurally similar ligands 1 and 2, there is no significant direct effect of the ligand, but that an appreciable interaction between ligand and temperature is present.

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